

EMMETT VS. THALER

CAUSE #308 2219

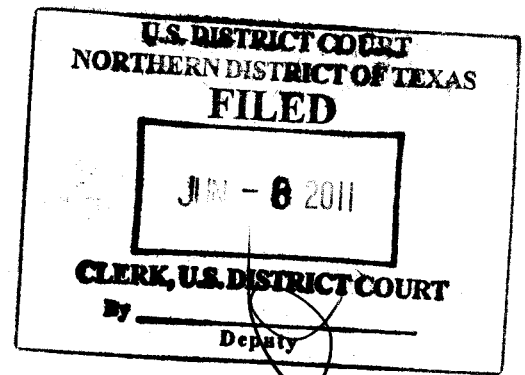
ORIGINAL

MOTION FOR RULE 60(B) #3 & #6

1. Please consider petitioner's expert report under rule 60 #2 & #3 & #6.
2. This is new evidence pursuant to Gonzales vs. Crosby 126. Ct. Pages 1685, 2103

Respectively submitted,

Barry Patrick Emmett II



JUNE 6, 2011

UNITED STATES DISTRICT COURT
1100 COMMERCE ROOM 14A20
DALLAS, TX. 75242

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March 29, 2011

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Evaluation of the Case of Barry Patrick Emmett, II

I. Purpose and Conclusions

Barry Patrick Emmett, II, often called Patrick, was born 12.27.76. This report will evaluate the mental effects on Mr. Emmett of taking chlorpromazine (Thorazine) 600 mg per day at the time of his sentencing hearing on 7.21.06. At that time, Mr. Emmett had been diagnosed at various times with schizophrenia, bipolar disorder and psychosis, and was described at times as suffering from hallucinations. The dose of 600 mg per day is at the upper recommended limits (300-600 mg) for treating these disorders in modern times.¹

Chlorpromazine is the original neuroleptic and antipsychotic drug, discovered in France in 1952 and in use throughout the western world by 1954.² Because it is the original and in many ways model antipsychotic drug, chlorpromazine's effects on brain and behavior have been most thoroughly studied in animals and humans. Like nearly all of the drugs called antipsychotics, chlorpromazine blocks neurotransmission in a particular system of neurotransmitters called dopamine. Dopamine nerves make up the largest trunk of nerves projecting from deeper in the brain into the frontal lobes. Blocking these nerves reduces the function of the highest centers of the brain in the frontal lobes, including both the ability and the motivation to weigh choices, to plan, to organize thoughts, and to come to rational decisions. In particular, this suppression of the frontal lobes results in apathy or indifference—an inability to care about oneself and one's situation, and an inability to assert oneself in a self-determined or autonomous fashion.

There is incontrovertible scientific and clinical evidence that chlorpromazine produces lobotomy-like effects that compromise will power, reduce motivation and produce psychological indifference, or apathy. These effects would be have been significantly incapacitating at a dose of 600 mg per day in regard to Mr. Emmett asserting his will power and making choices in everyday activities, let alone life-determining decisions such as a plea bargain. These effects occur in normal or disturbed individuals and even in animals, and would have occurred in Mr. Emmett regardless of his overall mental condition or diagnosis at the time.

Anyone receiving this high dose of chlorpromazine would be significantly impaired if not wholly impaired in regard to making independent or autonomous decisions. Cognition, memory or understanding may be relatively intact; but spontaneous activity, self-assertion, interest and involvement in one's own activities and life, or independent decision making and action will be reduced or crushed. In many cases, robotic behavior is induced. The individual can initiate very little spontaneous activity, and becomes docile and easily led.

This induction of apathy and this stifling of self-generated thought or activity is well-known to clinicians who work with patients prescribed large doses of antipsychotic

¹ Decades ago, larger doses were sometimes used.

² The terms antipsychotic drug and neuroleptic drug will be used synonymously. The older term "neuroleptic" meant "grabbing the neuron" and was intended to emphasize the neurotoxic effects of this class of drugs.

drugs. As we shall see, these effects have been frequently and graphically described in the scientific literature for more than half a century.

Unlike other medications, the antipsychotic drugs can cause these subduing effects on frontal lobe function without causing noticeable sedation or other apparent signs of toxicity. In a situation in which an individual is expected to act in an inhibited, controlled or docile fashion, such as during sentencing in a courtroom, the drug effects may go unnoticed.

Sometimes these subduing mental effects are accompanied by a more obvious slowing of bodily movements. The individual's gait often becomes slightly stooped, shuffling or stiff. Facial expressions may stiffen, so that the individual looks expressionless. Especially at higher doses, the antipsychotic drugs frequently produce this Parkinsonism syndrome in an obvious manner. However, when the individual is shackled and led slowly in a somber fashion into the courtroom, the effects upon gait and facial expression may not be so apparent.

Because this report is narrowly focused on the effects of this specific medication dose on any individual, Mr. Emmett's personal and alleged criminal history will not be evaluated. I chose not to interview Mr. Emmett because his subjective impressions of his condition were not necessary to reach a conclusion and I did not want to give the mistaken impression that I was in any way relying upon them. Anyone receiving a daily dose of 600 mg of chlorpromazine would suffer from the drug's typical suppressive effects upon mental life.

II. Background of the Expert

My Resume is also attached (**Appendix A**).

I am a psychiatrist licensed to practice medicine in New York State. I also have inactive licenses in Virginia, Maryland, and Washington DC. I was in the full-time private practice of psychiatry from 1968 to 2002, in Washington, DC and Maryland; and in November 2002, I moved to Ithaca, New York, where I am continuing all of my clinical and forensic activities. I am a Life Member of the American Psychiatric Association. I have a special interest and expertise clinical psychopharmacology, including medication adverse effects.

I have written more than 20 professional books and several dozen peer-reviewed professional articles. A number of my books, book chapters, and professional articles deal with adverse medication effects such as mental, behavioral, and neurological abnormalities caused by medications, including those caused by the drug in this case, chlorpromazine. Three of my medical textbooks specifically focus in depth on the adverse effects of the chlorpromazine and similar drugs:

Breggin, P. *Psychiatric Drugs: Hazards to the Brain* (1983). New York: Springer Publishing Company.

Breggin, P. *Brain-Disabling Treatments in Psychiatry* (1997). New York: Springer Publishing Company.

Breggin, P. *Brain-Disabling Treatments in Psychiatry, Second Edition* (2008). New York: Springer Publishing Company.

Also specifically concerning the neuroleptic medication in this case, I have written several peer reviewed scientific articles, including the following two:

Breggin, P. "Parallels between neuroleptic effects and lethargic encephalitis: The production of dyskinesias and cognitive disorders." *Brain and Cognition* 23:8-27, 1993. See **Appendix B** for complete article.

Breggin, P. "Brain damage, dementia and persistent cognitive dysfunction associated with neuroleptic drugs: evidence, etiology, implications." *Journal of Mind Behavior* 11:425-464, 1990. See **Appendix C** for complete article.

I have special training and considerable forensic experience, and I have also written extensively about interpreting scientific data concerning adverse drug effects, including the use of the FDA's spontaneous reporting system. In addition to my books, the following peer reviewed article is especially relevant to those issues:

Breggin, P. "Analysis of adverse behavioral effects of benzodiazepines with a discussion of drawing scientific conclusions from the FDA's Spontaneous Reporting System." *Journal of Mind and Behavior* 19: 21-50, 1998.

I also have considerable forensic and scientific experience in regard to the interpretation of FDA labels and have written about this in numerous sources, including these more recent articles:

Breggin, P. "Recent U.S., Canadian and British regulatory agency actions concerning antidepressant-induced harm to self and others: A review and analysis." *Ethical Human Psychology and Psychiatry*, 7: 7-22, 2005. Simultaneously published in the *International Journal of Risk and Safety in Medicine*, 16:247-259, 2005.

Breggin, P. "Recent regulatory changes in antidepressant labels: Implications for activation (stimulation) in clinical practice." *Primary Psychiatry*, 13, 57-60, 2006.

My work has influenced the FDA labeling of drugs and helped motivate the FDA to require the manufacturers of all neuroleptics to place a class label for tardive dyskinesia in the labels of their drugs.

I founded the peer-review journal *Ethical Human Psychology and Psychiatry* and I am on the editorial board of several other journals as well, including the *International Journal of Risk and Safety in Medicine*. I am frequently called upon to lecture or to

consult on the subject of adverse drug effects, including chlorpromazine. For example, in November 1998, I was invited by the National Institutes of Health (NIH) to be the scientific presenter on adverse drug effects in children at the national Consensus Development Conference on The Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder. I have been a consultant to the Federal Aviation Agency (FAA) on the adverse effects of psychiatric drugs on pilots. In 2008 I was the primary witness before the U. S. House of Representatives Committee on Veterans Affairs concerning the hazards of prescribing psychiatric drugs to combat troops (video available on www.breggin.com).

III. Materials reviewed

Medical Record, Parkland Health & Hospital System at Dallas County Jails.
Psychiatric Evaluations by David Mackie, RN, MN, ANP at ADAPT, 3.25.05, 4.14.05, 5.19.05.
Psychiatric Evaluation by Lisa K. Clayton for a report to the court. Undated. Fax stamp and cover letter dated 6.28.06.
Letter to attorney Lalon Peale from Lisa K. Clayton, MD, June 6, 2006.
Letter from Charles Kasbarian, MD, addressed to "To Whom It May Concern," 4.7.06.
Petition for a Writ of Habeas Corpus, Barry Patrick Emmett, II, Petitioner, vs. Nathaniel Quarterman, Director, Texas Department of Criminal Justice, Institutional Division.
Affidavits of Jackie Lane, Kelly Williams, W. T. Williams, Sr., Barbara A. Williams, Barry Emmett (father), and Mireille Emmett (mother). Also, non-affidavit statement of Dolores E. Jones (aunt).

IV. Evidence that Mr. Emmett was Taking Chlorpromazine at the Time of his Sentencing Hearing on July 21, 2006

Early in 2005 Mr. Emmett was placed on a variety of medications, including briefly on chlorpromazine. Later in the year he was prescribed the drug on a regular basis through the time of the hearing.

At ADAPT on 7.16.05 Mr. Emmett was reported to be on chlorpromazine 100 mg twice a day, along with other psychiatric drugs. On 7.20.05 he returned to the clinic with severe abnormal movements almost certainly due the chlorpromazine. The note said, "Per Dr. Reid-EPS classic for Thorazine."

EPS stands for Extrapyrarnidal Symptoms. These are caused by the same blockage of dopamine nerves that simultaneously causes the mental apathy and indifference. The term EPS often includes the Parkinsonian syndrome with shuffling or stiff gait and flatted facial expression that were described in Part I of this report. His dose at this time was one-third the size of the dose he would be taking at the hearing.

The drug was discontinued. On 7.20.05 a mental health form confirmed "Thorazine locks up jaw even with Cogentin." This indicates that the chlorpromazine (Thorazine) remained toxic to his nervous system even when he was treated with a medication, Cogentin, which tends to relieve the symptoms.

Mr. Emmett's adverse drug reactions continued on other neuroleptics. On 8.7.05 the Thorazine was restarted at 100 mg twice a day. Despite adverse reactions, he was continued on Thorazine 100 mg twice a day as indicated by notes on 8.20.05 and 9.7.05. However, he continued to have manic symptoms. These manic symptoms were probably caused or exacerbated by the unfortunate simultaneous prescription of nortriptyline, an antidepressant that causes manic symptoms. To control these symptoms, Mr. Emmett's dose of chlorpromazine was doubled to 200 mg twice a day on 10.20.05. The medical record indicates that he was continued on this dose on 10.26.05, 11.2.05, and 1.2.06.

On 1.29.06 Mr. Emmett continued to suffer from manic symptoms, including "racing thoughts," almost certainly caused or exacerbated by nortriptyline. At this time on 1.29.06 the antidepressant was finally discontinued and the dose of chlorpromazine was increased. The following is the exact instruction in the jail medical record: "Increase dose Thorazine [chlorpromazine] 300 mg 3 BID # 180." This dose (three 300 mg tablets twice a day) would have given him an overdose of 1800 mg but was hopefully not implemented. The intent was probably to order 300 mg twice a day for a total of 600 mg. It is possible that he did briefly endure an accidental massive overdose at this time; but the intended dose was more than sufficient to produce the drug's typical subduing effects on mental life.

On 3.2.06 Mr. Emmett was described as taking chlorpromazine 300 mg twice a day for a total of 600 mg per day. Subsequent medical record notes indicated that he remained on this dose on 3.20.06, 3.22.06, 4.19.06, 4.20.06, and 6.14.06.

On 6.28.06 a Psychiatric Evaluation by Lisa K. Clayton stated, "Understands charges against him." Dr. Clayton remarked, without noting the dose, "He currently is being given Thorazine in the Dallas County Jail and he stated it helps him sleep." In reality, he was being treated for manic or psychotic symptoms and being given a much larger dose than would be used for sleep. Dr. Clayton's conclusions are compromised by her apparent lack of knowledge concerning the large dose of chlorpromazine that the patient was taking.

As described in detail in Part I, and as scientifically confirmed in Part IV below, it is not surprising that Mr. Emmett was found to "understand" the charges against him. The ability to understand a concept sufficiently to explain it to an interviewer is not likely to be grossly impaired by chlorpromazine. The ability to fully involve oneself or to assert oneself in regard to that understanding would be wholly undermined on 600 mg per day of chlorpromazine.

On 7.21.06 Mr. Emmett made his court appearance for sentencing.

On 7.31.06 the Dallas County Jail Mental Health Follow Up diagnosed Mr. Emmett with "psychosis NOS [not otherwise specified]" and continued him on 600 mg per day of Thorazine.

This documentation from the jail medical record brackets the time of his sentencing and confirms that Mr. Emmett was taking a large dose of chlorpromazine 600 mg per day at the time of the sentencing. He had been exposed to this large dose for approximately six months. It also indicates that the dose had at times caused the expected significant and obvious neurological symptoms called EPS. It also indicates that the psychiatrist who declared that Mr. Emmett understood the charges against him had no idea that he was taking a very large dose of a drug that produces indifference, lack of motivation and reduced free will. Furthermore, in a setting in which docility is

expected—a psychiatric evaluation during incarceration—Mr. Emmett’s lack of self-determination would not have been immediately apparent without clinical probing. Also, it is entirely possible that Mr. Emmett understood or comprehended the charges against as reflected in his ability to explain or to describe them to an interviewer; but he was unable to come to decisions on his own behalf and to fully exert his will or to pursue his bests interests in his legal case and in the courtroom. In short, there is a huge difference between being able to explain an idea or a concept when asked to do so and being able to act upon that knowledge in a self-determined, autonomous and self-interested manner.

V. Chlorpromazine (Thorazine) Diminishes Motivation, Autonomy, Spontaneous Activity, and the Capacity to Assert Oneself

A. Clinical and Scientific Descriptions of Chlorpromazine Effects on Patients

Chlorpromazine (Thorazine) was first introduced into North America in 1954. As a result, the most in depth reports concerning its clinical effects appear in the mid- to late 1950s. These clinical descriptions remain valid today. The following review of the scientific literature is modified from my medical book, *Brain-Disabling Treatments in Psychiatry, Second Edition* (2008), as well as from two of my scientific peer-reviewed articles (Breggin 1993 and 1990; reproduced in **Appendices B and C**).

I have described these effects as “deactivation” (Breggin, 2008, pp. 21-44) of the frontal lobes with resultant indifference and lack of motivation or will power.

The term deactivation will be used to designate a continuum of phenomena variously described as disinterest, indifference, diminished concern, blunting, lacking of spontaneity, reduced emotional reactivity, reduced motivation or will, apathy, and, in the extreme, a rousable stupor. (Breggin, 2008, p. 32).

As noted in Part I, chlorpromazine is the original antipsychotic or neuroleptic drug, and so its effects have been studied in much more depth than later drugs in the same class. The very first report on the psychiatric use of chlorpromazine was published in France by Delay and Deniker (1952; translated in Jarvik, 1970). Their article described the actual state of the medicated patient for a medical world that as yet had no familiarity with the drug:

Sitting or lying, the patient is motionless in his bed, often pale and with eyelids lowered. He remains silent most of the time. If he is questioned, he answers slowly and deliberately in a monotonous, indifferent voice; he expresses himself in a few words and becomes silent. (Jarvik, 1970)

They also described the patient as “fairly appropriate and adaptable. . . . But he rarely initiates a question and he does not express his anxieties, desires or preferences” (Jarvik, 1970). As Delay and Deniker put it, there is an “apparent indifference or the slowing of responses to external stimuli” and “the diminution of initiative and anxiety” (Jarvik, 1970).

In a retrospective, the co-pioneer in the field, Deniker (1970), further emphasized what he considered to be the primary impact of chlorpromazine, the drug he had helped to discover:

But the impact of the most significant finding was not immediately recognized. It was the characteristic psychomotor *indifference* that chlorpromazine caused in treated subjects. Later, it was classified as akinesia. (italics added, p. 158).

As a result of this drug-induced "indifference," the individual, such as Mr. Emmett, may appear normal, especially in a highly controlled setting where compliance is expected. Nonetheless, he is fundamentally changed and vastly limited in regard to motivation and free will.

Lehmann and Hanrahan (1954) published the first article in English promoting its psychiatric use. They stated:

The aim is to produce a state of motor retardation, emotional indifference, and somnolence, and the dose must be increased accordingly as tolerance develops.

The doses required for achieving "retardation," "emotional indifference," and "lethargy" in this study rarely exceeded 800 mg/day,³ and sometimes did not exceed 100 mg/day. Mr. Emmett was on 600 mg per day.

Lehmann and Hanrahan (1954) go on to say:

The patients under treatment display a lack of spontaneous interest in the environment . . . they tend to remain silent and immobile when left alone and to reply to questions in a slow monotone. . . . Some patients dislike the treatment and complain of their drowsiness and weakness. Some state they feel "washed out," as after an exhausting illness, a complaint which is indeed in keeping with their appearance.

Lehmann and Hanrahan (1954) recognized that they were suppressing their patients without specifically affecting or improving symptoms such as hallucinations and delusions: "We have not observed a direct influence of the drug on delusional symptoms or hallucinatory phenomena."

The following year, Lehmann (1955) published his second article on chlorpromazine. With relatively small doses, he found the primary brain-disabling effect: "Many patients dislike the 'empty feeling' resulting from the reduction of drive and spontaneity which is apparently one of the most characteristic effects of this substance." He also spoke of "lassitude" and compared the effects to lobotomy: "In the management of pain in terminal cancer cases, chlorpromazine may prove to be a pharmacological substitute for lobotomy."

³ As noted in Part I, several decades ago the maximum dose of chlorpromazine was sometimes higher than 600 mg per day. Most of the patients in this study were receiving similar or lower doses than the 600 mg given to Mr. Emmett, and many received much lower doses.

The first British report concerning chlorpromazine as a psychiatric treatment (Anton-Stephens, 1954) confirmed the impact of the drug using small doses (200 mg/day), one-third the dose given to Mr. Emmett. Anton-Stephens called it "psychic indifference" and again compared it to lobotomy:

Psychic indifference. This is perhaps the characteristic psychiatric response to chlorpromazine. Patients responding well to the drug have developed an attitude of indifference both to their surroundings and their symptoms best summarized by the current phrase "couldn't care less." (p. 550)

Throughout the 1950s, some psychiatric texts continued to accurately describe the impact of the neuroleptics on the mind. Here, for example, is the lobotomy-like clinical picture of maximum benefit described by Noyes and Kolb in the 1958 edition of *Modern Clinical Psychiatry*:

If the patient responds well to the drug, he develops *an attitude of indifference both to his surroundings* and to his symptoms. He shows decreased interest in and response to his hallucinatory experiences and a less assertive expression of his delusional ideas. (p. 654, italics added)

This chemical straitjacketing, including flattening of emotion and motivation, has been called "akinesia"—technically meaning a lack of movement. It is one of the EPS side effects described in Part I and Part IV of this report and is associated with the slowing of mental processes that impedes decision making. Mayerhoff and Lieberman (1992) reported that the antipsychotic drugs caused a lobotomy-like "frontal lobe syndrome... consisting of affective flatness along with reduced motor and cognitive activity" (p. 129). They reviewed the scientific literature concerning loss of spontaneity and "apathy and difficulty with initiating usual activities," adding "It often goes unrecognized" (p. 128). These descriptions apply to the medication-induced incapacity of an individual like Mr. Emmett in regard to initiating efforts to advance his own interests with his lawyer and in the judicial hearing.

In clinical discussions, the lobotomy-like effects of the neuroleptics or antipsychotics are now sometimes subsumed under neuroleptic-induced deficit syndrome (NIDS). Malcolm Lader (1993), chairperson of an international symposium on the subject, wrote:

The benefits of treatment with classical neuroleptics are, however, obtained at the expense of a number of side effects, and many patients frequently complain of feeling "drugged" or drowsy and of being unable to concentrate; they lack motivation and are emotionally unresponsive: they also appear slow-moving and physically rigid. Some patients have complained of "feeling like a zombie." (p. 493)

In a paper titled "Neuroleptics and the neuroleptic-induced deficit syndrome," Lewander (1994a) and colleagues summarized:

The first central pharmacodynamic action of chlorpromazine to be described was sedation without narcosis. The antipsychotic action and extrapyramidal symptoms were observed later. Sedation can be separated into nonspecific sedation (drowsiness, somnolence) and specific sedation (psychomotor inhibition and psychic indifference). Both types are parts of the clinical profiles of classical neuroleptics. (p. 8).

In another paper, Lewander (1994b) described these effects as “the neuroleptic-induced deficit syndrome, commonly experienced with classical neuroleptics” (*italics added*, p. 64). It should be emphasized that these effects are “commonly experienced with classical neuroleptics.” Chlorpromazine is the epitome of the classical neuroleptic.

“Psychomotor inhibition and psychic indifference” are the key lobotomy-like effects that would have rendered Mr. Emmett, or anyone else, relatively unable to act upon his own behalf or to exert their volition.

In 1996 Jain devoted a section of his book to Neuroleptic-Induced Deficit Syndrome (NIDS), describing it as a syndrome that includes impairment of cognitive function (p. 138).

In 2007 psychiatrist J. Moncrieff reviewed my analysis of neuroleptic deactivation and confirmed its scientific validity. Moncrieff cited some of the literature that is also reviewed in this report and specifically noted the relationship to “frontal lobotomy” and “psychic indifference” (2007, p. 175).

In 2008 in the American Psychiatric Press *Textbook of Psychiatry* (Martinez et al., 2008) continued the same basic observations under the subject of neuroleptic-induced “akinesia:”

Akinesia is a behavioral state of diminished spontaneity characterized by decreased gestures, unspontaneous speech, apathy, and difficulty with initiating unusual activities. P. 1089

B. Chlorpromazine Impacts the Brain in a Similar Fashion in All People and Animals

As noted in Part I, these mentally disabling effects of chlorpromazine are not specific to an individual’s mental condition or even specific to the human species. The drug effect is caused by a direct impact on the normal (or abnormal) mammalian brain, involving inhibition of dopaminergic nerves—the main nerve pathway to the frontal lobes (Minzenberg, Yoon and Carter, 2008, p. 438; Martinez, Marangell, and Martinez, 2008, p. 1085; Breggin, 1990, 1993 & 2008).

Therefore, the drug effect is not specific for any disorder, such as schizophrenia, and affects normal individuals and even animals in an essentially like manner, by suppressing dopaminergic function in the brain. These drugs are used in a variety of settings to induce docility or placidity, including mental hospitals, prisons, and even in veterinary medicine (Breggin, 2008, pp. 38-40). None of the many studies cited in Part IV of this section found any difference in the drug effect that depended upon the mental condition or diagnosis of the individual. Although some professionals claim that these

drugs also have a specifically suppressive impact on psychotic symptoms, this is controversial. Meanwhile, there can be no doubt that medications like chlorpromazine reduce spontaneity, reduce autonomy, and reduce the ability to generate normal decision-making and action.

Writing in the most authoritative pharmacology textbook of the time, Jarvic (1970) summarized that neuroleptics produce indifference and "taming" in every species of animal studied. In the same vein in a later edition, Baldessarini (1985) stated that "Nearly all of the neuroleptic agents used in psychiatry can diminish spontaneous motor activity in every species of animal studied, including man" (p. 394). More specifically, he noted that "Exploratory behavior is diminished, and responses to a variety of stimuli are fewer, slower, and smaller" (p. 394).

Even normal volunteers suffer from the same chlorpromazine effects. In a 1991 editorial in *Biological Psychiatry* titled "Neuroleptic Dysphoria," Emerich and Sanberg described various adverse emotional reactions to neuroleptics, including "cognitive blunting." The editorial describes the experimental self-administration of the neuroleptic haloperidol by Belmaker and Wald (1977), in which each of these "normal experimental subjects" "complained of a paralysis of volition, lack of physical and psychic energy. The subjects felt unable to read, telephone or perform household tasks of their will, but could perform these tasks if demanded to do so." The editorial also mentioned reports of other mind-subduing effects, including "chemical straightjacketing," "lack of motivation," and a feeling "like a shade coming down."

Thus, the scientific literature is unequivocal in describing how chlorpromazine, even at much lower doses than given to Mr. Emmett, commonly produces a condition of apathy, indifference, lack of motivation, lack of spontaneous activity and lack of autonomy or self-determination that would render an individual incapable to making valid decisions in regard to important life events. It further confirms that these effects can easily go unnoticed. Like Mr. Emmett, the individual given neuroleptics may be able to respond to requests or guidance, while remaining limited in regard to motivation or initiative.

VI. Affidavits and Statements Describing Mr. Emmett's Mental Condition in Court

I did not rely on these statements in coming to my initial conclusions and did not need them to come to my final conclusions. The fact of Mr. Emmett was taking 600 mg of chlorpromazine at the time of his sentencing hearing was sufficient for me to determine beyond a reasonable degree of medical certainty that he would have been suffering from the lobotomy-like deactivation with suppressed emotions, motivation and will. However, the affidavits do confirm the descriptions of chlorpromazine effects that I have reviewed from the scientific literature, bolstered by my clinical observations.

(1) Jackie Lane, Mr. Emmett's aunt, reported that she saw Mr. Emmett in jail prior to the hearing and then again at the hearing on July 21, 2006, and that she and the family were "stunned by Patrick's debilitated state." She attributed his condition to Thorazine over-medication. She said that, before being asked, she told the attorney "Patrick was not Patrick" in the courtroom.

(2) Kelly Williams, Mr. Emmett's cousin, described Mr. Emmett's condition in court as "zombie-like." She believed he was in no position to make "such important decisions about his future." Notice that the term "zombie-like" also appeared in my review of the scientific literature as a description of chlorpromazine effects (see top of page 9, above).

(3) W. T. Williams, Mr. Emmett's uncle, was present at the sentencing hearing. He described Mr. Emmett as "disinterested," another word or concept that frequently used to describe chlorpromazine effects in the scientific literature.

(4) Barbara A. Williams, Mr. Emmett's aunt, was also present at the hearing. She stated, "...Patrick looked and behaved as though he was in a trance. When he spoke, his speech was flat-monotone. He had a detached demeanor and appeared in a stupor." This is an exact clinical description of the appearance of an individual under the influence of 600 mg of chlorpromazine per day.

(5) Barry Emmett, Mr. Emmett's father, was "shocked" by his son's appearance at the hearing and felt that he was "not mentally capable of understanding the gravity" of the situation. He did not provide details concerning his appearance.

(6) Mireille Emmett, Mr. Emmett's mother, was at the hearing. She stated, "He was obviously on some sort of mood altering medication that had even altered his physical appearance. He was bloated, lethargic and basically stupefied." The words "lethargic" and "stupefied" frequently appear in the literature describing chlorpromazine effects.

(7) Dolores E. Jones describes Mr. Emmett as "shuffling" into the courtroom. This could have been caused or exacerbated by shackles but as noted earlier in this report, it also describes a very typical chlorpromazine neurological effect (an EPS). It looked to her as if he had a "lobotomy," which is a remarkably accurate observation, since the drug causes similar effects by blocking frontal lobe function.

To a remarkable degree, descriptions of Mr. Emmett's appearance and behavior on the day of the hearing are entirely consistent with an individual who is suffering from the severe adverse mental and behavioral effects routinely associated with taking chlorpromazine 600 mg per day. The descriptions of Mr. Emmett actually contain words and concepts commonly found in the scientific literature.

VII. Conclusions

The following conclusions are made beyond a reasonable degree of medical certainty.

From 7.16.05 through his sentencing hearing on 7.21.06 Mr. Emmett was continuously taking the antipsychotic or neuroleptic drug chlorpromazine (Thorazine). Starting in 1.29.06 through the sentencing hearing Mr. Emmett was prescribed 600 mg

per day of the medication. This is the maximum adult dose for the treatment of psychosis which ranges from 300 mg to 600 mg (American Psychiatric Press, 2008, p. 1086).

Initially given in smaller doses for sleep, the drug was eventually given to him at various times for schizophrenia, bipolar disorder and psychosis.

The medication prescribed to Mr. Emmett in large doses—chlorpromazine (Thorazine)—has been known since its initial use in the mid-1950s to cause lobotomy-like indifference, loss of spontaneity or difficulty in initiating customary activities. Sometimes this has been discussed as a medication-induced lobotomy effect and at other times as a medication-induced akinesia or a Neuroleptic-Induced Deficit Syndrome (NIDS). As Lader described, in the extreme the effect becomes “zombie-like.” I have described the syndrome as “deactivation” in the scientific literature. Sometimes, but not always, the syndrome includes a suppression of movements—resulting, for example, in shuffling—as well as a suppression of emotions and motivation.

As noted in the scientific studies reviewed in this report and confirmed by clinical experience, an individual like Mr. Emmett taking the maximum 600 mg of chlorpromazine per day could not truly represent or express his self-generated, autonomous wishes in discussions leading up to his plea bargain or in a courtroom setting. Furthermore, his mental deficit in this regard might not be obvious or easily recognized, even by a trained professional observer, especially under courtroom conditions of physical and emotional restraint. The drug-induced docility and passivity would be mistakenly evaluated as voluntary cooperation. However, in Mr. Emmett’s case the drug effects were sufficiently obvious to be recognized and accurately described by those in the courtroom who knew him. This is not surprising given that he was prescribed the maximum dose of 600 mg per day and had been taking it continuously for six months.

It is not surprising that a psychiatric evaluation concluded that Mr. Emmett “understood” the charges against him. Chlorpromazine and other antipsychotic drugs do not grossly impair cognitive ability such as understanding and memory. Instead, chlorpromazine in large doses causes marked apathy and indifference and disables the individual’s capacity to make autonomous or self-determined decisions.

Mr. Emmett had various diagnoses including schizophrenia, bipolar disorder and psychosis with hallucinations. However, the science reviewed in this report makes clear that chlorpromazine drug effects are independent of an individual’s mental condition and even independent of the individual’s species. Individuals diagnosed with severe mental disorders, as well as normal human volunteers and animals, develop the same apathy and indifference, and loss of spontaneous activity. In Mr. Emmett’s case, he received a dose of sufficient size to profoundly deactivate or subdue anyone’s mental processes and behavior.

In conclusion, at the time of his sentencing hearing on 7.21.06, Mr. Emmett had been prescribed the maximum dose of chlorpromazine, 600 mg per day, for the previous six months up to and including the day of the trial. Without exception, this maximum dose of chlorpromazine would produce a disabling degree of apathy and indifference, vastly reducing anyone’s ability to make decisions, to generate his own opinions, or to assert himself on his own behalf. The medication slowed down Mr. Emmett’s mental and physical processes, making him sluggish, and it suppressed his emotions, making him unable to actively participate in critical life decisions. This dose of 600 mg of

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chlorpromazine per day would render any individual unable to actively pursue or to effectively assert his interests with his lawyer or at a judicial hearing.

Peter R. Baggett MD

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Moncrieff, J. (2007). Understanding psychotropic drug action: The contribution of the brain-disabling theory. *Ethical Human Psychology and Psychiatry*, 9, 170-179.

Noyes, A. P., and Kolb, L. C. (1958). *Modern Clinical Psychiatry* (5th ed.). Philadelphia: Saunders.

Appendices

A. Resume of Peter R. Breggin, MD

B. Breggin, P. R. (1993). Parallels between neuroleptic effects and lethargic encephalitis: The production of dyskinesias and cognitive disorders. *Brain and Cognition*, 23, 8-27.

C. Breggin, P. R. (1990). Brain damage, dementia and persistent cognitive dysfunction associated with neuroleptic drugs: Evidence, etiology, implications. *Journal of Mind and Behavior*, 11, 425-464.

Resume and Bibliography

Peter R. Breggin, M.D.

I. BACKGROUND HIGHLIGHTS

Harvard College (Cambridge) (1954-58):

Graduated with Honors

Directed Harvard-Radcliffe Mental Hospital Volunteer Program.

Research grants from Harvard Medical School and the National Institute of Mental Health (NIMH).

Co-authored 1st professional book, College Students in a Mental Hospital (1962).

Case Western Reserve School of Medicine (Cleveland) (1958-1962):

Conducted four years of psychopharmacology lab research with controlled animal trials supported by NIMH grant, resulting in first two published papers in psychopharmacology.

Special four-year individual tutorial with pediatrician Benjamin Spock, M.D.

Diplomat, National Board of Medical Examiners (1963):

Highest grade in country (99%) on psychiatry portion of boards used to qualify for medical licenses.

Massachusetts Mental Health Center (Boston) (1963-64):

First Year Resident in Psychiatry at the main Harvard teaching hospital.

Teaching Fellow at Harvard Medical School.

State University of New York Upstate Medical Center (Syracuse) (1962-63, 1964-66):

Intern in Mixed Medicine and Psychiatry.

Second and Third Year Resident and Teaching Assistant in Psychiatry.

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National Institute of Mental Health (NIMH) and U. S. Public Health Service Officer
(Charlottesville, VA and Bethesda, MD) (1966-68):

Full-time NIMH Consultant in Building and Staffing Community Mental Health Centers (1966-67).

Full-time NIMH Consultant in Mental Health and Education (1967-68).

University of Maryland (1968-1970):

Faculty, courses in counseling department.

Washington School of Psychiatry (1968-1972):

Faculty, courses for school counselors.

George Mason University (1990-96):

Adjunct Professor of Conflict Analysis and Resolution, courses on brain and behavior.

Johns Hopkins University (1996-99):

Faculty Associate in the Department of Counseling and Human Services, courses including psychopharmacology and diagnosis in psychiatry.

State University of New York (SUNY), Oswego (2007-2008, 2010-present):

Visiting Scholar in the Department of Education, Division of Counseling and Psychological Services, courses including psychopharmacology and psychotherapy (2007-2008).

Adjunct Professor, course on Empathic Therapy (2010-present).

II. HIGHLIGHTS OF PROFESSIONAL ACTIVITIES

Private Practice of Psychiatry, Ithaca, New York. (2003-present):

In November 2002, all of my professional activities (see below) moved to Ithaca, New York.

Private Practice of Psychiatry, Washington, DC and Bethesda, MD. (1968-2002):

Full-time private practice with individuals, couples and families with children.

Subspecialty clinical psychopharmacology and the drug approval process.

Founder and Director, Center for the Study of Empathic Therapy, Education and Living (www.empathictherapy.org), 2010-present:

This new nonprofit organization led by Dr. and Mrs. Breggin has a large Advisory Council that includes many psychiatrists, neurologists, psychologists, social workers and counselors, including professors and heads of department. Many public advocates and interested citizens also participate. The Center offers a free newsletter, a professional network, and an annual Empathy Therapy Conference. Dr. Breggin's many decades of reform work have led others to call him "The Conscience of Psychiatry." He continues his reform work with renewed emphasis on finding better, empathic approaches to helping children and adults in emotional distress.

Founder and Director, International Center for the Study of Psychiatry and Psychology (1972-2002) and Director Emeritus (2002-2010):

Dr. Breggin, joined by his wife in the 1980s, developed this first professional organization devoted to psychiatric reform.

Editor-in-Chief (1998-2002) and Founding Editor and Consultant (2002-present) of *Ethical Human Sciences and Services: An International Journal of Critical Inquiry*. Now entitled *Ethical Human Psychology and Psychiatry*.

Founded and edited a peer-reviewed journal with 40 contributing editors published by Springer Publishing Company.

Psychiatric Consultant (2010-present)

Integrative Counseling Center, Inc., Oswego, New York (a private clinic)

Editorial Consultant:

International Journal of Risk and Safety in Medicine
The Psychotherapy Patient
Journal of Critical Psychology, Counselling and Psychotherapy: Journal of the
Psychology and Psychotherapy Association
The Humanistic Psychologist
Journal of Mind and Behavior
Hospital and Community Psychiatry (reviewer in past)

Scientific Presenter at Conferences, Grand Rounds, Universities:

Selected Recent Presentations

U.S. House of Representatives, Committee on Veterans Affairs, February 24, 2010, Washington, DC, Hearings chaired by Rob Filner (D-CA) on

"Exploring the Relationship Between Medication and Veteran Suicide," 35-minute lead off testimony on "Antidepressant-Induced Suicide and Violence: Risks for Military Personnel." Audio of complete hearings and written presentations available on www.breggin.com.

17th Annual International Military and Civilian Combat Stress Conference, Los Angeles, May 1-2, 2009. Pre-conference full-day workshop on "Clinical Psychopharmacology: Efficacy and Alternatives" and Plenary on "Does Psychiatric Medication Increase the Risk and Prevalence of Suicide?"

Past Presentations

Hundreds of invited scientific presentations on psychopharmacology, shock treatment, psychosurgery, psychotherapy, and legal issues, including to the National Institutes of Health (NIH) Consensus Development Conferences on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder (November 1998); the NIH Consensus Development Conference on Electroconvulsive Therapy (1985); National Institutes of Health Panel on NIH Research on Anti-social, Aggressive and Violence-related Behaviors and Their Consequences (1994); National Institute of Mental Health (NIMH) Guest Speakers Program; U.S. House of Representatives Committee on Education (September 2000); American Psychiatric Association; NIH Institute on Hospital and Community Psychiatry; American Psychological Association; American Orthopsychiatry Association; American Autism Society; American Association for the Advancement of Science; American Counseling Association, Connecticut Psychiatric Society Residents Program, Harvard University School of Education Special Lecture; Georgetown University School of Medicine Department of Pharmacology; New Jersey Medical School Department of Psychiatry Annual Medical Forum; Walter Reed Army Hospital Psychiatric Residency Program; National Naval Medical Center; Metropolitan Hospital Center/New York Medical College Department of Psychiatry; Manhattan State Hospital (New York City) Grand Rounds; Spring Grove Hospital (Maryland) CME Credit Seminars; Chestnut Lodge Hospital Case Conference; St. Elizabeths Hospital Grand Rounds and Seminars (Washington, DC); Regents College of Psychotherapy and Counseling (London); Institute for Genetics (Cologne); Royal Ottawa Hospital Grand Rounds (Canada); MIND of Great Britain; University of Sheffield Department of Psychiatry (England).

Special Presentations and Advanced Training Courses related to Clinical Psychopharmacology:

I have presented at and/or attended a number of lengthy several-day-long training workshops on the drug approval process that dealt with the FDA approval process and drug labeling. The following seminars, including several at which I made presentations, dealt extensively with adverse drug reactions, drug development, labeling and related processes:

- (1) "Regulatory Training Course I: IND [Investigative New Drug] Phase."

A course in how drug companies develop an IND for the FDA in accordance with FDA statutes, regulations, and guidelines. DIA (Drug Information Association). Bethesda, Maryland, February 26-28, 1996.

(2) "Future development of neuroleptic medications: A report to the FDA." This was a report to an FDA Meeting of the Psychopharmacologic Drugs Advisory Committee concerning labeling issues and the future development of neuroleptic medications. It was published as "Future development of neuroleptic medications: A report to the FDA" in the Rights Tenet (Newsletter of the National Association for Rights Protection and Advocacy) Fall 1995.

(3) "Regulatory Training Course II: Marketing Application & Post Approval Phase." A course in how drug companies develop an NDA [New Drug Application], as well as post-approval activities, in accordance with FDA statutes, regulations, and guidelines. DIA (Drug Information Association), Bethesda, Maryland, March 27-29, 1996.

(4) "Clinical Therapeutics and the Recognition of Drug-Induced Disease: How Health Care Professionals and the FDA Can Work Together to Reduce the Risks of Adverse Drug Events." A workshop focused on the spontaneous reporting system presented by the Center for Drug Evaluation and Research (CDER) of the FDA, Georgetown University School of Medicine, Washington DC, June 10, 1994.

(5) "The Application of GCP [Good Clinical Practices] for Study Site Coordinators and Business Administrators." Described as "a comprehensive, practical overview of the responsibilities of the investigator, the clinical study coordinator assisting the investigator, and the sponsor in the conduct of a clinical trial" for FDA approval of a drug. DIA (Drug Information Association), Philadelphia, December 11-13, 1995.

(6) "Pharmaceutical Industry Crisis Management Workshop." Purpose described as "to develop the participants knowledge of the fundamental elements of crises and crisis management in the pharmaceutical industry." Initial day covered handling of a variety of issues, including New Drug Applications (NDAs), FDA regulations and industry relations, recalls, adverse drug event reporting, and clinical trial standards. DIA (Drug Information Association), Washington, DC, December 4, 2000.

(7) "Ritalin Litigation." Described as "The medical and legal roadmap to trying or defending your Ritalin suit successfully," including presentations on stimulant drug treatment, ADHD, and the role of the FDA and DEA in monitoring industry activities. I presented on "The science behind the lawsuits" (including labeling issues) and also attended. The American Conference Institute, New York City, March 29, 2001.

(8) "Emerging Drug Litigation Conference." One-half day on class action suits at which I presented on "The Science and Medicine of Ritalin" (including labeling issues) and also attended. Mealey's (Lexis/Nexis). New Orleans, May 17, 2001.

(9) "Adverse Effects of SSRI Medications: A Medical Legal Conference." Labeling was a key issue at this conference focused on product liability. I presented on "Adverse Psychiatric Effects of SSRI Antidepressants" (including labeling issues) and attended conference. Extant Medical Legal Consulting. Philadelphia, October 4-5, 2002.

(10) "SSRI-Induced Stimulation, Suicidality and Violence in Children and Adults." These were public presentations to two FDA Advisory Committee meetings on modifying the labeling for SSRI-induced suicidality in children. Each meeting involved the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee. I summarized evidence for a stimulant syndrome that causes suicidality and violence that should be included in the label. The label changes later adopted by the FDA closely parallel my suggestions in my presentations and publications. Bethesda, Maryland, February 2, 2004 and September 13, 2004.

(11) "Anti-Depressant Suicidality and Violence: More about Deception than Science. Observations Made at the FDA Hearings Press Conference, sponsored by the Alliance for Human Research protection (AHRP)." I address issues surrounding what kind of material gets into FDA-approved labels, including the limitations of that data. Other presenters discussed related issues. Bethesda, Maryland, September 14, 2004.

(12) "Stimulation, Violence and Suicide as Adverse Reactions to SSRIs in Children and Adults." Public Presentations and attendance at two FDA Advisory Committee meetings on modifying the labeling for SSRI-induced suicidality in children (three days total). Each meeting involved the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee. I summarized evidence for a stimulant syndrome that causes suicidality and violence that should be included in the label. The label changes later adopted by the FDA closely parallel my suggestions in my presentations and publications. Bethesda, Maryland, February 2, 2004 and September 13, 2004.

(13) "Anti-Depressant Suicidality and Violence: More about Deception than Science. Observations Made at the FDA Hearings Press Conference, sponsored by the Alliance for Human Research protection (AHRP)." I address issues surrounding the quality of the data drug companies generate and what ultimately gets into FDA-approved labels. Other presenters

discussed related issues. Bethesda, Maryland, September 14, 2004.

Medical Expert and Researcher:

I have testified in more than 70 cases since the early 1970s, including criminal, malpractice, and product liability. They often involve psychopharmacology and adverse drug effects, neuroleptic-induced tardive dyskinesia, SSRI-induced violence and suicide, and psychosurgery and ECT-induced brain damage.

Some of the suits in which I have been involved, and some of research I have published, resulted in changes being made in the FDA-approved labels for neuroleptics and SSRI antidepressants.

A few highlights include:

(1) Medical expert in *Kaimowitz v. Department of Mental Health*, Wayne County, Michigan (1973). The three-judge panel followed my testimony in an opinion that helped to stop lobotomy and psychosurgery in the state and federal facilities around the country. This is considered a landmark case in the history of psychiatry and the law.

(2) Medical expert for the 100 or more combined Prozac product liability suits (1992-1994) against Eli Lilly, including the famous Wesbecker trial (Fentress et al.) that the drug company secretly settled in a controversial manipulation of the court system.

(3) Medical expert and consultant in many tardive dyskinesia malpractice and product liability suits.

(4) Medical expert in numerous criminal cases with defenses based on involuntary intoxication with psychiatric drugs.

(5) Invited Scientific Presenter on adverse drug effects in children at the November 1998 National Institutes of Health (NIH) Consensus Development Conference on the Diagnosis and Treatment of Attention Deficit Disorder.

(6) Medical consultant for the FAA (Federal Aviation Agency) concerning effects of SSRIs on pilots (1998-2000).

(7) Testimony before the Food and Drug Administration (FDA) on the dangers of SSRI antidepressants in children (February 2004). The published opinion of the FDA panel closely paralleled my testimony and publications about the overall risk of stimulation (activation) with the potential for agitation, violence and suicide.

Memberships:

Current:

American Psychiatric Association (Life Member)
Canadian Psychiatric Association
World Association of Medical Editors

Until approximately 2005-6
Royal Society of Medicine
Regulatory Affairs Professionals Society (RAPS)
Drug Information Association (DIA)
American Psychological Association
American Orthopsychiatric Association (Fellow)

Medical Licenses:

New York State, Washington, D.C., Maryland, and Virginia (last three inactive)

III. PROFESSIONAL BOOKS

1. College Students in a Mental Hospital: Contribution to the Social Rehabilitation of the Mentally Ill (New York, Grune & Stratton, 1962) (jointly authored by Carter Umbarger, James Dalsimer, Andrew Morrison, and Peter Breggin).
2. Electroshock: Its Brain-Disabling Effects (Springer, NY, 1979).
3. Psychiatric Drugs: Hazards to the Brain (Springer, NY, 1983).
4. Toxic Psychiatry (St. Martin's, NY, 1991).
5. Beyond Conflict (St. Martin's, NY, 1992).
6. Talking Back to Prozac (with Ginger Breggin) (St. Martin's, NY, 1994).
7. The War Against Children (with Ginger Breggin) (St. Martin's, NY, 1994).
8. Psychosocial Approaches to Deeply Disturbed Persons (senior editor) (Haworth Press, NY, 1996).
9. Brain-Disabling Treatments in Psychiatry: Drugs, Electroshock and the Role of the FDA (Springer, NY, 1997).
10. The Heart of Being Helpful: Empathy and the Creation of a Healing Presence (Springer, NY, 1997; new paperback edition in 2006).
11. Talking Back To Ritalin (Common Courage Press, ME, 1998).
12. The War Against Children of Color: Psychiatry Targets Inner City Children. (Common Courage Press, ME, 1998) (with Ginger Breggin) Revision and update of The War Against Children.
13. Your Drug May Be Your Problem: How and Why To Stop Taking Psychiatric

Medications. (Perseus Books, Cambridge, MA, 1999) (Co-authored by David Cohen, Ph.D.).

14. Reclaiming Our Children: A Healing Solution to a Nation in Crisis. (Perseus Books, Cambridge, MA, 2,000).

15. Talking Back to Ritalin, Revised Edition. (Perseus Books, Cambridge, MA, 2001).

16. The Antidepressant Fact book. (Perseus Books, Cambridge, MA, 2001)

17. Dimensions of Empathic Therapy (jointly co-edited by Ginger Breggin and Fred Bemak) (Springer Publishing Company, NY, 2002).

18. The Ritalin Fact Book. (Perseus Books, Cambridge, MA, 2002).

19. Your Drug May Be Your Problem: How and Why To Stop Taking Psychiatric Medications, Second Edition. (Perseus Books, Cambridge, MA, 2007) (Co-authored by David Cohen, Ph.D.).

20. Brain-Disabling Treatments in Psychiatry: Drugs, Electroshock and the Psychopharmaceutical Complex, Second Edition (Springer Publishing Company, NY, 2008).

21. Medication Madness: The Role of Psychiatric Drugs in Cases of Violence, Suicide, and Crime. (St. Martin's Press, NY).

22. Wow, I'm an American! How to Live Like Our Nation's Heroic Founders. (Ithaca, NY; Lake Edge Press).

IV. PEER-REVIEWED PUBLICATIONS

1. "The Psychophysiology of Anxiety." Journal of Nervous Mental Diseases 139:558-568, 1964.

2. "Coercion of Voluntary Patients in an Open Hospital." Archives of General Psychiatry 10:173-181, 1964. Reprinted with a new introduction in Edwards, R.B. (ed): Psychiatry and Ethics. Buffalo, Prometheus Books, 1982, and in Edwards, R.B. (ed): Ethics of Psychiatry. Amherst, New York, Prometheus Books, 1997.

3. "The Sedative-like Effect of Epinephrine." Archives of General Psychiatry 12:255-259, 1965.

4. "Psychotherapy as Applied Ethics." Psychiatry 34:59-75, 1971.

5. "Therapy as Applied Utopian Politics." Mental Health and Society 1:129-146,

1974.

6. "Psychiatry and Psychotherapy as Political Processes." American Journal of Psychotherapy 29:369-382, 1975.

7. "Madness is a Failure of Free Will; Therapy Too Often Encourages It." Psychiatric Quarterly 53:61-68, 1981. Originally published (in French) in Verdiglione A (ed): La Folie Dans La Psychoanalyse. Paris, Payot, 1977.

8. "Electroshock Therapy and Brain Damage: The Acute Organic Brain Syndrome as Treatment." Behavior and Brain Sciences 7:24-25, 1984

9. "Neuropathology and Cognitive Dysfunction from ECT." Psychopharmacology Bulletin 22:476-479, 1986.

10. "Ellettroshock: Tra Rischioiatrogeno e Mito Terapeutico." (P. Breggin and G. de Girolamo) Quaderni Italiani di Psichiatria 6:497-540, 1987.

11. "The Three Dynamics of Human Progress: A Unified Theory Applicable to Individuals, Institutions and Society." Review of Existential Psychology and Psychiatry 21:(Nos. 1-3)97-123, 1988-89.

12. "Precious the Crow." Voices (Journal of the American Academy of Psychotherapists) 23:32-42, Summer 1987.

13. "Brain Damage, Dementia and Persistent Cognitive Dysfunction Associated with Neuroleptic Drugs: Evidence, Etiology, Implications." Journal of Mind Behavior 11:425-464, 1990.

14. "Psychotherapy in the Shadow of the Psycho-Pharmaceutical Complex," Voices (journal of the American Academy of Psychotherapists) 27:15-21, 1991

15. "A Case of Fluoxetine-induced Stimulant Side Effects with Suicidal Ideation Associated with a Possible Withdrawal Syndrome ('Crashing')." International Journal of Risk & Safety in Medicine 3:325-328, 1992

16. "Parallels Between Neuroleptic Effects and Lethargic Encephalitis: The Production of Dyskinesias and Cognitive disorders." Brain and Cognition 23:8-27, 1993.

17. "A Biomedical Programme for Urban Violence Control in the US: The Dangers of Psychiatric Social Control." (Peter Breggin and Ginger Ross Breggin). Changes: An International Journal of Psychology and Psychotherapy 11, No. 1 (March):59-71, 1993.

18. "Psychiatry's Role in the Holocaust." International Journal of Risk and Safety in Medicine 4:133-148, 1993. Adapted from a paper delivered at "Medical Science

Without Compassion" in Cologne, Germany and published in the conference proceedings.

19. "Should the Use of Neuroleptics Be Severely Limited?" Changes: An International Journal of Psychology and Psychotherapy 14:62-66 March 1996.

20. "The Hazards of Treating 'Attention-Deficit/Hyperactivity Disorder' with Methylphenidate (Ritalin)" (coauthored by Ginger Breggin) Journal of College Student Psychotherapy 10:55-72, 1996.

21. "Psychotherapy in Emotional Crises without Resort to Psychiatric Medication." The Humanistic Psychologist 25:2-14, 1998.

22. "Analysis of Adverse Behavioral Effects of Benzodiazepines with a Discussion of Drawing Scientific Conclusions from the FDA's Spontaneous Reporting System." Journal of Mind and Behavior 19:21-50, 1998.

23. "Electroshock: Scientific, ethical, and political issues." International Journal of Risk & Safety In Medicine 11:5-40, 1998.

24. "Psychostimulants in the treatment of children diagnosed with ADHD: Part I—Acute risks and psychological effects." Ethical Human Sciences and Services 1:13-33, 1999.

25. "Psychostimulants in the treatment of children diagnosed with ADHD: Part II—Adverse effects on brain and behavior." Ethical Human Sciences and Services 1:213-241, 1999.

26. "Psychostimulants in the treatment of children diagnosed with ADHD: Risks and mechanism of action." International Journal of Risk and Safety in Medicine, 12 (1), 3-35, 1999. (Simultaneously published version of #'s 24 and 25)

27. "Empathic self-transformation and love in individual and family therapy." Humanistic Psychologist, 27:267-282, 1999.

28. "What psychologists and psychotherapists need to know about ADHD and stimulants." Changes: An International Journal of Psychology and Psychotherapy 18:13-23, Spring 2000

29. "The NIMH multimodal study of treatment for attention-deficit/hyperactivity disorder: A critical analysis." International Journal of Risk and Safety in Medicine 13:15-22, 2000. Also published in Ethical Human Sciences and Services.

30. "Empowering social work in the era of biological psychiatry." (2001) [The annual Ephraim Lisansky lecture of the University of Maryland School of Social Work.] Ethical Human Sciences and Services 3:197-206.

31. "Fluvoxamine as a cause of stimulation, mania, and aggression with a critical analysis of the FDA-approved label." International Journal of Risk and Safety in Medicine, 14: 71-86, 2002. Simultaneously published in Ethical Human Sciences and Services, 4, 211-227, 2002.

32. "Psychopharmacology and human values." Journal of Humanistic Psychology, 43: 34-49, 2003.

33. "Suicidality, violence and mania caused by selective serotonin reuptake inhibitors (SSRIs): A review and analysis." International Journal of Risk and Safety in Medicine, 16: 31-49, 2003/2004. Simultaneously published in Ethical Human Sciences and Services 5:225-246, 2003.

34. "Recent U.S., Canadian and British regulatory agency actions concerning antidepressant-induced harm to self and others: A review and analysis." Ethical Human Psychology and Psychiatry, 7, 7-22, 2005. Simultaneously published in the International Journal of Risk and Safety in Medicine, 16, 247-259, 2005.

35. "Recent regulatory changes in antidepressant labels: Implications for activation (stimulation) in clinical practice." Primary Psychiatry, 13, 57-60, 2006.

36. "Court filing makes public my previously suppressed analysis of Paxil's effects." Ethical Human Psychology and Psychiatry, 8, 77-84, 2006.

37. "How GlaxoSmithKline suppressed data on Paxil-induced akathisia: Implications for suicide and violence." Ethical Human Psychology and Psychiatry, 8, 91-100, 2006.

38. "Drug company suppressed data on paroxetine-induced stimulation: Implications for violence and suicide." Ethical Human Psychology and Psychiatry, 8, 255-263, 2006.

39. "Intoxication anosognosia: The spellbinding effect of psychiatric drugs." Ethical Human Psychology and Psychiatry, 8, 201-215, 2006. Simultaneously published in the International Journal of Risk and Safety and Medicine, 19, 3-15, 2007.

40. "ECT damages the brain: Disturbing news for patients and shock doctors alike." Ethical Human Psychology and Psychiatry, 9, 83-86, 2007.

41. Exposure to SSRI antidepressants in utero causes birth defects, neonatal withdrawal symptoms and brain damage." (Co-author, Ginger Breggin). Ethical Human Psychology and Psychiatry, 10, 5-9, 2008.

42. "Homicidal ideation causally related to therapeutic medications." (Donald Marks, Peter Breggin, and Derek Braslow). Ethical Human Psychology and Psychiatry.

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10, 134-145, 2008.

43. "Antidepressant-induced suicide, violence, and mania: Risks for military personnel." *Ethical Human Psychology and Psychiatry*, 12, 111-121, 2010.

APPENDIC B.

Breggin, P. R. (1993). Parallels between neuroleptic effects and lethargic encephalitis: The production of dyskinesias and cognitive disorders. *Brain and Cognition*, 23, 8-27.

BRAIN AND COGNITION 23, 8-27 (1993)

Parallels between Neuroleptic Effects and Lethargic Encephalitis: The Production of Dyskinesias and Cognitive Disorders

PETER R. BREGGIN

Center for the Study of Psychiatry and George Mason University

A retrospective examination of lethargic encephalitis finds many parallels with neuroleptic effects. The encephalitis, like the neuroleptics, produced an acute continuum of cognitive disorders from emotional indifference through apathy and onto a rousable stupor. It also produced similar acute dyskinesias, including akinesia, akathisia, dystonia, oculogyric crises, and tremors. The encephalitis also caused similar chronic effects, including dementia and psychosis, and somewhat different persistent dyskinesias. The chronic motor and cognitive disorders, like those associated with the neuroleptics, were often delayed in onset. An acute, severe episode of lethargic encephalitis also finds a parallel in the neuroleptic malignant syndrome. These parallels are probably due to a common site of action in the basal ganglia. They provide a model for understanding many neuroleptic effects and alert us to the probability of persistent cognitive deficits, including dementia, from neuroleptic treatment. © 1993 Academic Press, Inc.

Increasing concern is being shown about acute and persistent cognitive deficits associated with neuroleptic therapy. Thus far the literature has lacked a comprehensive model or framework for explaining the source, nature, and course of these deficits. Parallels between the effects of lethargic encephalitis and neuroleptic treatment offer a potential model based on a common site of impact in the basal ganglia and associated structures, resulting in both motor and cognitive disorders. These close parallels draw our attention to the probability of persistent cognitive dysfunction following chronic neuroleptic treatment.

LETHARGIC ENCEPHALITIS

Lethargic encephalitis (LE, encephalitis lethargica, von Economo's disease, and epidemic encephalitis) was identified by von Economo in

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the winter of 1916–1917 in Vienna. The pandemic was most severe in Europe and North America, with cases reported throughout the world. Over a decade, the disease afflicted more than a million people and caused hundreds of thousands of fatalities (Ravenholt and Foege, 1982). The last epidemic was reported in 1926 (Matheson Commission, 1939) and the disease largely disappeared by 1930. The infectious nature of LE was demonstrated with its transmission to monkeys, but the presumed viral agent was never isolated or identified.

Manifestations of the disease varied greatly from case to case and epidemic to epidemic: but the syndrome frequently included lethargy or a rousable stupor, various cognitive and behavioral abnormalities, and dyskinesias, among them hyperactivity, tremor, chorea and athetosis, dystonia, and Parkinsonism (Abrahamson, 1935; Brill, 1959; von Economo, 1931; Ward, 1986). Neurological symptoms due to involvement of the basal ganglia¹ were far more common than those associated with the cerebral cortex.

The disease could result in complete recovery or, in approximately 25% of the cases, death (Jubelt & Miller, 1989). Often it became chronic without any period of recovery. At other times, the patient seemed to recover: but months or years later developed postencephalitic disorders afflicting both the mental faculties and motor control, most frequently Parkinsonism. On occasion, postencephalitic states seemed to develop in the absence of a recognized acute phase (von Economo, 1931, p. 112).

Good reasons exist to compare lethargic encephalitis effects with those of neuroleptic drugs. The encephalitis caused a much broader spectrum of acute and chronic symptoms than those associated with neuroleptics; not all manifestations of the infectious disease will be found in neuroleptic-treated patients. *However, nearly all the cognitive and motor disorders commonly associated with neuroleptic treatment were also commonly associated with lethargic encephalitis.*

Some empirical research was carried out on cognitive function in post-encephalitic cases (e.g., Worster-Drought and Hardcastle, 1924–1925); however, it was not sufficiently extensive for comparative purposes. Evaluation of cognitive dysfunction from LE will draw on clinical observations and perspectives.

In the early years of the epidemic, some clinicians mistakenly diag-

¹ The term basal ganglia includes several large gray masses of neurons embedded in the lower parts of each cerebral hemisphere, including the striatum. The striatum is made up of the caudate and the lenticular nuclei, the latter being divided into the putamen and the globus pallidum. When the term basal ganglia is used in this review, it will also include the substantia nigra which sends afferent dopaminergic fibers to the striatum via the nigrostriatal pathway. Damage to the dopaminergic neurons of the substantia nigra affects the striatum. The basal ganglia are interconnected with the reticular activating system, the limbic system, and the frontal cortex (Alheid, Heimer & Switzer, 1990).

nosed LE as dementia praecox or schizophrenia, and even referred to it as "epidemic schizophrenia" (Wyatt, Kirch, & De Lisi, 1989, p. 720). von Economo (1931, p. 133) observed that confusions between encephalitis and schizophrenia occurred "in the days preceding our knowledge of encephalitis lethargica." These confusions affected the concept of schizophrenia in the early 20th Century. Sarbin (1990) observes that many of Kraepelin's and Bleuler's patients diagnosed with dementia praecox and schizophrenia were in reality displaying postencephalitic neurological symptoms.

Discussing the differential diagnosis, Brill (1959, p. 1168) observes, "the emotional reaction is shallow and often dull and apathetic" in encephalitic patients, "but it does not resemble schizophrenia . . ." Ward (1986, p. 219) confirms that "a picture closely resembling schizophrenia was unusual," and adds, "Comparisons between the phenomenology of encephalitis lethargica and schizophrenia suggested that basal ganglia pathology might be the basis of schizophrenia, but such generalizations tend to be far-fetched" (p. 221). Indeed, "Encephalitis is clearly recognizable in necropsy material whereas schizophrenia is not" (Boardman, 1990, p. 185).²

In this paper, it is suggested that the more accurate comparison is between LE and neuroleptic treatment, both of which damage the basal ganglia and produce similar acute and chronic clinical syndromes.

EARLY COMPARISONS BETWEEN THE NEUROLEPTIC AND THE ENCEPHALITIC EFFECTS

Psychiatrists and neurologists working in the 1950s often had firsthand experience with patients from the earlier LE epidemic and were able to

² The finding of extrapyramidal motor disorders in preneuroleptic clinical descriptions of schizophrenia has led some researchers to conclude that at least some motor disorders are the product of schizophrenia rather than the neuroleptics (Waddington & Crow, 1988). As already noted, these preneuroleptic era cases were probably misidentified examples of lethargic encephalitis or other coincident diseases of the basal ganglia or associated structures (also see, for example, Appel, Myers, & Morris, 1958, p. 549). The cases were almost always state mental hospital patients who were exposed to a wide variety of potentially brain-damaging contingencies, including epidemic diseases, malnutrition, trauma, or toxic therapies. As noted in the text, there is no known connection between schizophrenia and basal ganglia disease. When damage to the basal ganglia and surrounding structures is identified on autopsy, a diagnosis other than schizophrenia is made. The same confusion originally occurred between schizophrenia and general paresis before the Wassermann test (Bellak, 1948, p. 88). The question of whether or not tardive dyskinesia is almost always the result of neuroleptic treatment, rather than a mental disorder, is largely answered by a recent controlled study involving the elderly. Older people are considered most susceptible to spontaneous dyskinesias; but during a 24-month period, more than 40% of a neuroleptic-treated group (65 years or older) developed tardive dyskinesia, while none of the controls did so (Yassa, Nastase, Camille, & Belzile, 1988).

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compare its effects to those of the neuroleptics. Delay and Deniker, who pioneered the psychiatric use of neuroleptics in France in the 1950s, recognized certain similarities between LE and the new drugs (Delay, Deniker, & Thuillier, 1957).

It is certain that the observation of "cerebral accidents" due to prochlorperazine brings back to life an entire pathology observed as sequelae of lethargic encephalitis, especially in the preparkinsonian excito-motor phase, where abnormal movements and mental states dominated. (p. 509).

In a retrospective published in 1970, Deniker explained:

It was found that neuroleptics could experimentally reproduce almost all the symptoms of lethargic encephalitis. In fact, it would be possible to cause true encephalitis epidemics with the new drugs . . . Furthermore, it might have been feared that these drugs, whose actions compares with that of encephalitis and parkinsonism, might eventually induce irreversible secondary neurological syndromes. (1970, pp. 160, 163).

Other clinicians and researchers became aware of parallels between the effects of the viral disease and the medication (Paulson, 1959). In a 1957 symposium, Haase (1959, p. 199) drew comparisons between LE and neuroleptic effects. Haase also compared the neuroleptic effect to the "analogous syndromes of encephalitis lethargica" and postulated a common lesion in the striatum of the basal ganglia (cited in Kline, 1959, p. 472). Brill (1959) also recognized similarities between LE and the neuroleptics, "which, in full doses, can reproduce many of the most outstanding features of the chronic encephalitic syndrome" (p. 1166), including Parkinsonian rigidity, masked facies, tremor, restlessness, oculogyric crises, dystonias, and "the rousable stupor of acute encephalitis" (p. 1167). Hunter, Earl, and Thornicroft (1964) also recognized similarities and suggested that neuroleptic-treated patients suffer from a "chemically induced" encephalitis.

SIX PARALLEL EFFECTS

At least six parallels between both the acute and the persistent effects of neuroleptics and LE can be drawn: (1) *acute* extrapyramidal reactions or dyskinesias, including Parkinsonism, akathisia, dystonia, chorea, atetosis, and tremors; (2) *acute* cognitive dysfunctions such as apathy, disinterest, and reduced arousal; (3) *chronic* (irreversible) motor disorders, including tardive dyskinesia, tardive akathisia, and tardive dystonia; (4) *chronic* (irreversible) cognitive dysfunctions, including dementia, anosognosia, and deactivation¹; (5) the close resemblance between neuroleptic

¹ The term deactivation will be used to designate a continuum of phenomena variously described as disinterest, indifference, diminished concern, blunting, lack of spontaneity,

malignant syndrome (NMS) and an acute episode of LE: (6) the common site of action in the basal ganglia.

ACUTE EXTRAPYRAMIDAL REACTIONS

Several extrapyramidal symptoms manifested themselves in the acute phase of LE. These so closely paralleled the various motor disorders routinely produced by neuroleptic medications that they can be discussed together.

LE patients frequently suffered from compulsive hyperactivity, an "irritative hyperkinetic form" of the disease (Haase, 1959). von Economo (1931) considered the "hyperkinetic form" the second most frequent acute manifestation of the disease. This hyperactivity was typically associated with a subjective feeling of extreme tension or anxiety, what von Economo described as "general mental unrest and ceaseless motor activity" (p. 36). An identical hyperkinesia, called akathisia, is very common in drug-treated patients. In a sample of 110 patients, Van Putten (1975) found a rate of 45% "some time during the course of their treatment" (p. 45). Van Putten, May, and Marder (1974) found that akathisia developed in 75% of patients after 1 week of receiving a daily 10-mg dose of haloperidol.

During the onset of the disease, LE patients commonly developed a Parkinsonian syndrome, including psychomotor retardation, akinesia, masked facies, tremor, and a characteristic shuffling gait. von Economo (1931) considered this "amyostatic-akinetic" form the third most frequent acute manifestation of the disease. In chronic postencephalitic states, the Parkinsonian syndrome was by far the most common. A very similar Parkinsonian syndrome is also common during acute and prolonged neuroleptic therapy and can probably be induced in any patient with sufficiently high doses. Some phases of the viral epidemic were more marked by akinesia and others by hyperkinesia, with a considerable crossover (von Economo, 1931). Similarly, according to Van Putten (1975), "59% of [neuroleptic-treated] patients with akathisia concomitantly experienced akinesia, parkinsonian tremor, or dystonia" (p. 45).

Frequently, acute encephalitic patients developed dystonias: painful, tonic spasms of the voluntary muscles. Oculogyric crises—spasmodic eye deviations lasting for minutes or hours—were among the most common dystonias (von Economo, 1931). Dystonias are more rare during neuroleptic treatment and usually occur within the first days or weeks. However, when drug-induced dystonias do develop, they are often oculogyric. Delay et al. (1957) reported disabling "hypertonic" dystonias, in-

reduced emotional reactivity, reduced motivation or will, apathy, and, in the extreme, a rousable stupor.

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cluding eye deviations, in response to prochlorperazine, a neuroleptic that is especially prone to produce them. They compared these reactions to similar reactions reported by Marinesco, Radovici, and Drăgănescu (1925) in association with LE. Paulson (1959) attributed the occurrence of oculogyric crises in both encephalitis and drug treatment to dysfunction of the basal ganglia.

In summary, the two most common dyskinesias associated with routine neuroleptic therapy—Parkinsonism and akathisia—were also among the most frequently associated with the early or acute stages of LE. Dystonias, including oculogyric crises, while more common in LE, are also occasionally found in neuroleptic treatment.

A CONTINUUM OF ACUTE COGNITIVE DYSFUNCTIONS

A continuum of deactivation was reported as a consistent and prominent feature of LE, ranging from disinterest through a rousable stupor, and was the subject of considerable discussion. The same continuum was cited as the primary effect of neuroleptic treatment by pioneers in the field, but in recent years has received insufficient attention.

von Economo (1931) noted that when roused from the stupor, many LE patients were docile and obeyed commands, without displaying gross cognitive dysfunction (p. 27).

If aroused, they wake up quickly and completely, are oriented and fully conscious, and can reply sensibly to questioning; they are fully aware of the situation, carry out all requests promptly, get up if asked to do so and walk about, but, left to themselves, soon drop back to sleep. (p. 27).

In his section discussing "Psychological Disorders," von Economo spoke of two basic dysfunctions generally found in LE: "disturbances of will," characterized by a "dynamic lack of impulse," and "Changes of 'humor'," with "indifference" and "lack of emotion" (p. 162). Abrahamson's 1920 descriptions of the effects of viral encephalitis, reprinted in his posthumous book, *Lethargic Encephalitis* (1939), also cover the continuum from disinterest through rousable stupor.

Irritability both to internal and external stimuli diminishes, and the vital tone of the afflicted host lessens. . . . He may display neither conscious nor unconscious initiative. . . . Yet from the depth of this seeming slumber, he may respond immediately when questioned and his short but coherent answers show no loss either of memory or of orientation. . . . There is a complete lack of emotional expression. . . . The face, waxen and corpse-like, remains an impassive and inscrutable mask. . . . In other words, sensory stimuli stream into the brain and the brain ignores them. . . . [And] volition is practically suspended. (pp. 32-41)

Abrahamson and von Economo both believed that the cognitive dysfunction were part of a unitary syndrome that included motor inhibition or slowing. In effect, patients lost the will to move. In connecting the

loss of will and diminished movement, von Economo referred to "akinesia" (p. 159), a term now used in psychiatry to describe the similar neuroleptic effect that includes both motor slowing and apathy (Van Putten, May, & Wilkins, 1980). For his part, Abrahamson used the term "psychomotor inertia" (p. 40), nearly identical to the phrase commonly used in contemporary psychiatric rating scales, i.e., the BPRS' "psychomotor retardation."

More recently, Ward (1986) confirmed the characteristic continuum of cognitive disorder in association with LE, including "subjective feelings of marked lassitude" and a general "lack of initiative" (p. 217). Ward also notes the lack of clinically apparent cognitive deficits.

A very similar continuum of cognitive dysfunction was reported in the earliest clinical descriptions of the neuroleptic effect. In 1952 Delay and Deniker described for the first time the effect of chlorpromazine when given in relatively small doses. The effect varied from indifference to the rousable stupor. Later, Deniker (1970) more fully appreciated the central role of drug-induced *indifference*.

But the impact of the most significant finding was not immediately recognized. It was the characteristic psychomotor indifference that chlorpromazine caused in treated subjects. Later, it was classified as akinesia. (p. 158).

Other investigators quickly pinpointed indifference as the main clinical effect of the drug. The first description of this effect in the North American literature was by Lehmann and Hanrahan (1954) who focused on "emotional indifference." They observe, "Patients receiving the drug become lethargic" (p. 230). The first British report, by Anton-Stephens (1954), states:

Psychic indifference. This is perhaps the characteristic psychiatric response to chlorpromazine. Patients responding well to the drug have developed an attitude of indifference both to their surroundings and their symptoms best summarized by the current phrase "couldn't care less." (p. 550)

Textbooks from the beginning of the neuroleptic era also focused on the production of indifference or disinterest as the primary drug effect. For example, in *Modern Clinical Psychiatry*, Noyes and Kolb (1958) commented: "If the patient responds well to the drug, he develops an attitude of indifference both to his surroundings and to his symptoms" (p. 654). From Germany, Flugel identified what he called "the akinetic-avolitional syndrome" as key to the neuroleptic effect (Kline, 1959, p. 466).

Jarvic (1970) summarized that neuroleptics produce indifference and "taming" in every species of animal studied. Lehmann (1975) suggested that neuroleptic treatments result primarily "in reduced reactivity to external and internal stimuli and in decreased spontaneous activity" and in "blunting of emotional arousal" (p. 28). Without elaborating on it, he used the phrase "deactivation of the CNS" (p. 32) to describe the overall

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effect. Emerich and Sanberg (1991) noted that neuroleptics produce many types of dysphoria, including "cognitive blunting" and a "paralysis of volition" (p. 201). A number of authors have observed the apathy so frequently associated with long-term neuroleptic treatment (Van Putten & May, 1978; Van Putten et al., 1980). There are many discussions of psychomotor slowing, often without specifically addressing the deactivation component. Baldessarini (1985) states that "Nearly all of the neuroleptic agents used in psychiatry can diminish spontaneous motor activity in every species of animal studied, including man" (p. 394). More specifically, he notes that "Exploratory behavior is diminished, and responses to a variety of stimuli are fewer, slower, and smaller . . ." (p. 394). Consistent with this, Breggin (1983a, pp. 56-59, 1991) has taken the viewpoint that neuroleptic-induced disinterest and lethargy are nonspecific for any particular diagnostic group of patients. Like many earlier clinicians and researchers, he believes that deactivation is largely responsible for the clinical effect of the neuroleptics.

CHRONIC MOVEMENT DISORDERS

Victims of LE frequently developed irreversible postencephalitic motor complications, of which Parkinsonism was the most common. Sometimes the Parkinsonism persisted continuously from the acute into the chronic stage, and sometimes it appeared years later after seeming recovery from an acute attack.

As early as 1959, Paulson observed:

When used in therapeutic doses, phenothiazines may never permanently injure the central nervous system. Their innocence, however, may be difficult to prove to a patient who develops idiopathic Parkinsonism years after having had identical symptoms as a side-effect of tranquilization. (p. 801)

There are few reports in the literature about irreversible Parkinsonism associated with neuroleptic therapy; but little attempt has been made to evaluate the possibility.⁴ Cases of persistent Parkinsonism have been reported following neuroleptic malignant syndrome (see ahead).

As another chronic residual of the viral disease, von Economo (1931, p. 107) noted "irritative phenomena," including "cases of hemichorea and also of general chorea, others reminiscent of athetosis, cases of torticollis, torsion-spasms, and tics." Similarly, in their discussion of chronic effects of LE, Noyes and Kolb (1958) also noted:

Tremors, tics, myotonias, and athetoid and choreiform movements are frequently observed. In addition to these dyskinesias and hyperkinesias, there may be parox-

⁴ Most long-term neuroleptic patients are undergoing drug treatment while being evaluated for persistent dyskinesias, and it is *assumed*, perhaps wrongly, that the frequent findings of akinesia and Parkinsonism is merely the result of the on-going treatment.

ysmal symptoms such as disturbances in rate and rhythm of respiration, also gasping and yawning. (p. 171).

A few years ago, these descriptions of persistent neuroleptic sequelae by von Economo and by Noyes and Kolb would have varied somewhat from our understanding of neuroleptic-induced sequelae. More recently attention has been given to irreversible hyperactivity (tardive akathisia) and irreversible torsion spasms (tardive dystonias) caused by neuroleptics (e.g., Gualtieri & Sovner, 1989; Burke, Fahn, Jankovic, Marsden, Lang, Gollomp, & Ilson, 1982), and the two syndromes are now finding their way into neurology textbooks (Fahn, 1989). Thus neuroleptic-induced tardive dyskinesia, tardive akathisia, and tardive dystonia are paralleled in the chronic disorders produced by encephalitis lethargica.

Tardive dyskinesia is a frequent sequela of neuroleptic therapy. The American Psychiatric Association's (1980) task force on tardive dyskinesia concluded that more than minimal signs of the disease are found in at least 40% of older patients on long-term neuroleptic treatment. More recent studies are disclosing higher rates than earlier studies, and Schatzberg and Cole (1986, p. 99) remark that 50–60% of chronically institutionalized patients display dyskinesias. Studies by Gualtieri (Gualtieri & Sovner, 1989) have found rates of 13–14% for tardive akathisia in institutionalized developmentally disabled persons with a history of neuroleptic treatment.

In summary, both LE and neuroleptic treatment result in high rates of chronic dyskinesias, with Parkinsonism more common as the aftermath of the viral disease, while tardive dyskinesia and tardive akathisia are more frequent following neuroleptic treatment.

CHRONIC COGNITIVE DYSFUNCTIONS

Several chronic cognitive disorders resulted from LE and are now found in association with long-term neuroleptic treatment.

Dementia and Persistent Cognitive Impairment

Dementia was among the most common chronic manifestations of the LE. Many of the Parkinsonian patients may have suffered from varying degrees of cognitive dysfunction and dementia. Harvey (1986) reports that Parkinsonism is associated with dementia in 20–80% of cases, depending upon the criteria. According to Yahr (1989), some authorities consider dementia "an intrinsic characteristic of the disease, increasing in severity as it progresses" (p. 662). Yahr himself concludes that "it does appear that a number of cognitive, perceptual, and memory deficits are present" in Parkinson's disease (p. 662).

The intellectual deficits in Parkinsonism patients have been somewhat hard to measure, because the dementia is dominated by pathology in the

basal ganglia rather than the cerebral cortex. This results in so-called subcortical dementia (Huber and Paulson, 1985) with fewer overt intellectual deficits. Like postencephalitic patients, those with subcortical dementia display more apathy and depression than euphoria, and social judgment is characteristically spared.

As a result of the more minimal intellectual deterioration, observers like von Economo and Abrahamson may have been less likely to describe the patients as obviously demented. Furthermore, it is plausible that the finding of postencephalitic dementia was considered too commonplace to merit much attention compared to the more dramatic psychomotor retardation and deactivation syndrome. Nonetheless, von Economo did describe cases of more typical dementia with "confusion," "delirium," and "para-amentia." He also compared the patients' mental condition to that of neurosyphilis, toxic states, and other disorders commonly associated with generalized intellectual dysfunction. Abrahamson (1935) reported that the typical akinetic syndrome sometimes deteriorated into frank dementia: "This state may pass away leaving confusion, faulty orientation and memory loss of the Korsakoff type" (p.35).

According to von Economo, an irreversible hypomanic syndrome resembling "moral insanity" was frequently seen, especially in younger patients. Usually it was moderate in degree: the patients became "more talkative, importunate, impertinent, forward, and disrespectful; they lack inhibition; they often become troublesome and antisocial and display a tendency to outbreaks of emotion" (1931, p. 128). The cases could develop progressively from the acute phase of encephalitis or appear at a later date. The clinical picture, in retrospect, seems like mild to moderate dementia with euphoria.

Do the neuroleptics cause parallel permanent changes in cognitive function? Evidence for neuroleptic-induced cerebral cortical atrophy, persistent cognitive dysfunction, and dementia has recently been discussed by a number of authors (e.g., Breggin, 1983a, 1990, 1991; Jones, 1985; Myslobodsky, 1986; and Gualtieri & Barnhill, 1988). In concluding that neuroleptic treatment frequently causes atrophy and dementia, Breggin (1990) reviewed brain scan studies, clinical evaluations, psychological testing, animal and human postmortem findings, and parallel models from other diseases of the brain, such as Parkinsonism and Huntington's chorea. Rates of cerebral atrophy in neuroleptic-treated patients range from 10 to 40%, and tend to correlate with life-time drug exposure.

Wilson, Garbutt, Lanier, Moylan, Nelson, and Prange (1983) for example, found mental abnormalities consistent with an organic brain syndrome in tardive dyskinesia patients. The severity of cognitive disability correlated with the severity of tardive dyskinesia symptoms. Some studies have correlated persistent cognitive dysfunction with tardive dyskinesia and with life-time intake of neuroleptics (DeWolfe, Ryan, & Wolf,

1988). Famuyiwa, Eccleston, Donaldson, and Garside (1979), and many others, have found cerebral atrophy as measured on a computerized tomography (CT) scan among neuroleptic-treated patients. Often the atrophy is associated with cognitive dysfunction. Gualtieri and Barnhill (1988) concluded:

In virtually every clinical survey that has addressed the question, it is found that TD patients, compared to non-TD patients, have more in the way of dementia. (p. 149)

I have evaluated several cases of long-term neuroleptic patients with hypomanic syndromes similar to those described by von Economo—mildly euphoric individuals who display superficial joviality, poor judgment, rambling talkativeness, and sometimes an inappropriate tendency to move too close to the examiner. Wilson, Garbutt, Lanier, Moylan, Nelson, and Prange (1983) have described a similar neuroleptic-induced syndrome that they call dysmentia, consisting of “unstable mood, loud speech, and [inappropriately close] approach to the examiner.” It is probably a variant of hypomanic dementia. Euphoria, as well as apathy, can result from frontal lobe damage and dysfunction (Bradley, Daroff, Feniichel, & Marsden, 1991, p. 84; see below).

In summary, there is evidence that varying degrees of dementia resulted from LE and that persistent cognitive dysfunction and dementia also result from long-term neuroleptic treatment. Usually, the dementia associated with the neuroleptics is of the subcortical variety with apathy and relatively little disturbance of higher cortical function. In addition, a hypomanic dementia was also identified as a consequence of LE and can also be found after prolonged neuroleptic treatment.

Anosognosia

Anosognosia—denial of dysfunction after physical damage to the higher centers of the brain—is frequently found in tardive dyskinesia. One-half or more of tardive dyskinesia patients deny the existence or severity of their involuntary movements (Breggin, 1983a, pp. 115–117; DeVaugh-Geiss, 1979; Myslobodsky, 1986). Some tardive dyskinesia victims will be able to identify symptoms of the disease in other patients but not in themselves (Smith, Kuchorski, Oswald, & Waterman, 1979). Anosognosia is said to be usually associated with damage to the parietal, nondominant hemisphere. However, patients with generalized brain disease, such as neurosyphilis and chronic alcoholism or Korsakoff’s syndrome, will often deny their impairments and confabulate. My experience coincides with that of Fisher (1989) who states that anosognosia “may qualify as one of the general rules of cerebral dysfunction” (p. 128).

The presence of anosognosia in tardive dyskinesia patients tends to confirm the existence of generalized cerebral dysfunction. It can be diffi-

cult, however, to distinguish anosognosia from the indifference or disinterest produced by neuroleptic treatment.

In the literature on LE, no references to anosognosia have been located. The specific symptom was probably obscured by the generalized apathy displayed by so many of the patients.

Deactivation and the Frontal Lobe Syndrome

von Economo (1931) and other observers noted that many LE patients lapsed into chronic apathy or indifference, often in association with Parkinsonian psychomotor retardation. This chronic deactivation is also common among tardive dyskinesia patients. Myslobodsky (1986) points out that many observers have wondered why so many tardive dyskinesia patients "develop signs of emotional indifference" and that no satisfactory explanation has been forthcoming. As already noted, Van Putten and May (1978) and Van Putten et al. (1980) have described the apathy that is characteristic of many long-term neuroleptic patients. These outcomes are probably best understood as a sometimes irreversible deactivation, compounded with anosognosia.

Deactivation can result from dysfunction in either the frontal lobes and limbic system (as an aspect of frontal lobe syndrome) or the basal ganglia (as an aspect of subcortical dementia). Adams and Victor (1989) divide the manifestations of frontal lobe syndrome into (1) cognitive and intellectual changes, such as loss of abstract reasoning and planning, (2) personality deterioration, and (3) "impairment or lack of initiative and spontaneity" (p. 333) or deactivation, which they call the most common effect of frontal lobe disease. Stuss and Benson (1986, 1987) ascribe two basic functions to the anterior portion of the frontal lobes: "sequence, set, and integration," and "drive, motivation, and will" (1986, p. 241). The "most common alteration is apathy" (p. 242). The activation function appears to depend upon medial frontal structures.

Much of what we know about the frontal lobe syndrome comes from studying the effects of psychosurgery, whose primary clinical effect is the production of deactivation or what Kalinowsky (1973, p. 20) called "diminished concern." Anosognosia is also common in postpsychosurgery patients who frequently deny they have been operated on, despite the evidence of surgical scars or burr holes (Breggin, 1981). My clinical experience indicates that most elements of the frontal lobe syndrome, including deactivation, are also produced by stereotactic procedures, such as cingulotomy, amygdalotomy, and thalamotomy, that impair the limbic system.

As already described, pioneers in the use of neuroleptics almost uniformly cited deactivation as the main clinical effect of neuroleptics (see above). Because of this, clinicians often referred to the neuroleptics as a

chemical lobotomy (Haase, 1959, p. 206). Bleuler (1979) observed that long-term neuroleptic use "also often dampens the vitality and the initiative of the person" (p. 301). He concluded, "So we see that long-term maintenance with neuroleptics is fraught with some of the same disadvantages that are ascribed to lobotomies" (p. 301).

Although there is little direct evidence, it is probably as Bleuler suggests, that long-term exposure to neuroleptics can produce an irreversible frontal lobe syndrome with deactivation. The syndrome would seem an inevitable consequence of the permanent dysfunction of dopaminergic neurons that frequently results from neuroleptic treatment (see below). Some of these neurons (from the ventral tegmentum) project to the limbic system and frontal lobes. Others (from the substantia nigra) project to the striatum where they also interconnect with the limbic system as well as with the reticular activating system (Alheid, Heimer, & Switzer, 1990).

Psychosis

Somewhat infrequently, postencephalitic patients developed schizophrenic-like psychoses, including confusion, hallucinations, and delusions (Brill, 1959). As discussed earlier, the syndrome was relatively easy to distinguish from schizophrenia.

Neuroleptic-treated patients have been reported to develop tardive psychoses (Jones, 1985; Chouinard, Jones, & Annable, 1978). I have noted these reactions on occasion when a patient quickly decompensates during the process of withdrawing from neuroleptics. These psychoses can sometimes be distinguished from the patients' premedication psychotic disorder which tends to return, if at all, several months after drug withdrawal. At present, tardive dementia is probably a more clearly discernable syndrome than tardive psychosis.

ACUTE ENCEPHALITIS AND THE NEUROLEPTIC MALIGNANT SYNDROME

Attention has been increasingly focused on an especially severe reaction, NMS, which occurs in a small percentage of neuroleptic-treated patients. A review of 24 episodes of NMS in 20 patients by Rosebush and Stewart (1989) found that most cases fit the following cluster of symptoms: delirium, a high fever with diaphoresis, unstable cardiovascular signs, an elevated respiratory rate, and an array of dyskinesias, including tremors, rigidity, dystonia, and chorea.

Patients spoke little during the acute illness and later reported that they had found themselves unable to express their anxiety and feelings of doom. Almost all patients were agitated shortly before developing NMS, suggesting to the authors that they were undergoing akathisia. The white blood cell count was elevated in all cases, dehydration was common, and

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lab tests showed a broad spectrum of enzymatic abnormalities. While this series had no deaths, the authors note that 20–30% of untreated cases reportedly die. This mortality rate corresponds with that of LE.

There seems to be nothing about acute NMS to distinguish it from an acute, severe episode of LE, except for the fact of antecedent neuroleptic therapy. Although Roscbush and Stewart provide insufficient data to draw exact parallels, their NMS patients also suffered similar chronic impairments to those reported in LE patients. Of the 20 patients, 14 continued to have “extrapyramidal symptoms or mild abnormalities of vital signs and muscle enzymes at the time of discharge” (p. 721); but we are not told how many of the 14 specifically had persistent extrapyramidal signs. In a striking parallel with LE, three patients displayed persistent Parkinsonian symptoms until they were lost to follow up. One patient, who had mild cognitive impairment prior to NMS, developed a persistent worsening of her dementia.

Recognition of the similarities between acute LE, severe LE, and NMS can help us in evaluating cases of NMS, sharpening awareness of possible persistent sequelae. The parallels may someday help elucidate the mechanisms of both.

LE AND NEUROLEPTIC IMPACT ON THE BASAL GANGLIA

While LE afflicted all regions of the brain, including the frontal cortex, there was consistent agreement that the most marked pathology was located in the basal ganglia and especially the substantia nigra (von Economo, 1931; Brill, 1959; Ward, 1986). According to Brill (1959), “The involvement of the substantia nigra is outstanding and may be seen by inspection, even in gross freshly cut specimens” (p. 1165).

There is also general agreement that the basal ganglia are most directly affected by the neuroleptics. As Thacker, Ferraro, Hare & Tamminga (1988) summarize, “basic research suggests that . . . all mammalian brains treated chronically with neuroleptic drugs develop DA [dopamine] receptor supersensitivity in the striatum” (p. 199) (also see Rupniak, Jenner, & Marsden, 1983). These striatal changes are due, at least in part, to the suppression or inactivation of dopaminergic neurons originating in the substantia nigra (White and Wang, 1983).

While there is a consensus that the neuroleptics impair neurotransmission in the basal ganglia, the nature and existence of related neuropathological lesions remain less certain. Cadet and Lohr (1989) review a variety of physiological changes in neuroleptic-treated animals, as well as post-mortem anatomical changes in tardive dyskinesia patients. They conclude, “We agree with the suggestion that these drugs may be responsible for degenerative changes in the basal ganglia . . .” (p. 181; see also Breggin, 1983a). Those few postmortem studies of tardive dyskinesia pa-

tients that are available usually show increased degeneration in the substantia nigra (Roizin, True, & Knight, 1959; Hunter, Blackwood, Smith, & Cumings, 1968; Christensen, Moller, & Faurbye, 1970; Jellinger, 1977). Other postmortem studies of schizophrenic patients have found increased dopamine receptor density in the basal ganglia (caudate and putamen) (reviewed in Hyde, Casanova, Kleinman, & Weinberger, 1991). Nearly all of these patients had been exposed to neuroleptics.

Another review (Breggin, 1990, pp. 447-450) focused on animals exposed to neuroleptic treatment and found consistent reports of basal ganglia pathology after several weeks or months. For example, Neilsen and Lyon (1978) documented cellular loss in the striatum of rats after 36 weeks and concluded "The results further suggest that persistent irreversible anatomical changes can follow long-term neuroleptic treatment" (p. 85). Pakkenberg, Fog and Nilakantan (1973) found basal ganglia degeneration in rats after 1 year of drug exposure.

Brain scan studies (CT and magnetic resonance imaging) of tardive dyskinesia patients have disclosed neuropathology, sometimes in the basal ganglia (Bartels & Themelis, 1983; Besson, Corrigan, Cherryman, & Smith, 1987). However, no consistent pattern has emerged from the limited number of studies (Rama Krishnan, Ellinwood, & Rayasam, 1988, p. 173).

Yahr (1989) observed that the dementia associated with Parkinsonism probably requires mesocortical, as well as striatal, dopamine deficits. Neuroleptic-induced dopamine depletion also afflicts both the nigrostriatal and the mesocortical or limbic projections, probably contributing to the production of both tardive dyskinesia and tardive dementia. Jenner and Marsden (1983, p. 234), for example, found that cerebral dopamine receptors became hyperactive after 6-12 months of continuous neuroleptic administration in rats and that the overactivity is associated with the development of abnormal behaviors.⁵

Gualtieri and Barnhill (1988) conclude that tardive dyskinesia is associated with dementia, and that the source of both problems, as is the case with Parkinson's disease and Huntington's chorea, is most likely lesions in the basal ganglia.

DISCUSSION

Probably because of their common impact on the basal ganglia, neuroleptic effects parallel many of the core symptoms reported in LE. In the acute phase, both produce a deactivation continuum from indifference to

⁵ Although the permanence of most cases of tardive dyskinesia points to a corresponding irreversible hyperactivity of dopamine receptors, it has not been demonstrated in the animal brain. However, animals are also less prone to develop tardive dyskinesia, and may therefore be less susceptible than humans to persistent receptor changes.